Title of research study: Effects of liposomal bupivacaine for acute pain in hip and femur fractures: a randomized, active comparator-controlled, blinded trial (Funded by the Department of Defense)

Investigator: Ian Brown, MD

Why am I being invited to take part in a research study?

We invite you to take part in a research study because you have been admitted to the University of California, Davis Medical Center with a femur and/or hip fracture.

What should I know about a research study?

(Experimental Subject's Bill of Rights)

- Someone will explain this research study to you, including:
  - The nature and purpose of the research study.
  - The procedures to be followed.
  - Any drug or device to be used.
  - Any common or important discomforts and risks.
  - Any benefits you might expect.
  - Other procedures, drugs, or devices that might be helpful, and their risks and benefits compared to this study.
  - Medical treatment, if any, that is available for complications.
  - Whether or not you take part is up to you.
- You can choose without force, fraud, deceit, duress, coercion, or undue influence.
- You can choose not to take part.
- You can agree to take part now and later change your mind.
- Whatever you decide it will not be held against you.
- You can ask all the questions you want before you decide.
- If you agree to take part, you will be given a signed and dated copy of this document**.**

Who can I talk to?

If you have questions, concerns, or complaints, or think the research has hurt you, talk to the research team at:

Attn: Dr. Ian Brown
University of California Davis Medical Center
Department of Surgery
Division of Trauma, Acute Care Surgery and Surgical Critical Care

2315 Stockton Blvd. Sacramento, CA 95817
Phone: (916) 734-1279

For non-emergency issues you can call the UCDMC Hospital Operator (916-734-2011), tell the Operator you are participating in a research study and you wish to talk to Dr. Ian Brown. In the case of an emergency, dial 911 from any phone.

This research has been reviewed and approved by an Institutional Review Board ("IRB"). Information to help you understand research is on-line at http://www.research.ucdavis.edu/policiescompliance/irb-admin/.You may talk to a IRB staff member at (916) 703-9151, IRBAdmin@ucdmc.ucdavis.edu, or 2921 Stockton Blvd, Suite 1400, Room 1429, Sacramento, CA 95817 for any of the following:

- Your questions, concerns, or complaints are not being answered by the research team.
- You cannot reach the research team.
- You want to talk to someone besides the research team.
- You have questions about your rights as a research subject.
- You want to get information or provide input about this research.

Why is this research being done?

The purpose of this study is to determine whether the use of FDA approved pain reliever liposomal bupivacaine (Exparel®) is effective for the surgical treatment of patients with hip and femur injury, compared to the currently used FDA approved pain reliever ropivacaine (Naropin®).

How long will the research last?

We expect that you will be in this research study for the duration of your hospital stay. Your participation in this study will not change the duration (either shorter or longer) of your hospitalization with the possible exception of unexpected adverse outcomes from the study drug.

How many people will be studied?

Thirty-four people at UC Davis Medical Center will be in this research study.

What happens if I say yes, I want to be in this research?

If you agree to take part in this research study, you will first be asked to sign this informed consent form before any procedures take place. You will be given a light blue wristband to wear.

The pain medication you receive will be chosen by chance, like flipping a coin. Neither you nor the study doctor will choose what treatment you get. You will be randomly put into a treatment group by chance to receive either:

- Liposomal Bupivacaine; or
- Ropivacine

You will have a 50% (1 in 2) chance of receiving liposomal bupivacaine (study drug) and a 50% (1 in 2) chance of receiving ropivacaine (standard of care pain medicine).

This is a double-blind study, which means neither you nor the study doctor will know if you are receiving liposomal bupivacaine or ropivacaine. However, in case of an emergency, the study doctor can get this information.

After you have given consent and have been assigned to a treatment group you will receive your local pain medication injection. This procedure involves injecting the medication into the tissue of the hip and thigh in side of your fracture. First your thigh will be washed and then sterile drapes will be placed. The physician will then use an ultrasound machine to guide placement of drug injection into muscle layers located in the hip and thigh. The injection will be administered as a single dose (once). Following the procedure, both treatment groups will be given an additional oral or IV pain medication as needed which will be determined by the study staff.

Your level of pain will be evaluated per standard of care by nurses at least every 4 hours (while you are awake) after receiving the medication. How you do overall is also part of the study.

During your research participation, information including your name and date of birth, fracture type, and pain medication will be collected. This data will be analyzed to see if liposomal bupivacaine is as effective as ropivacaine, the standard pain medicine.

After all data has been recorded, your identifying information will be removed, and the data will be stored in a de-identified manner to reduce the risk to you. Your participation will not be required after this.

What are my responsibilities if I take part in this research?

If you take part in this research, you will have no additional responsibilities. There is no time commitment being requested from you.

What happens if I do not want to be in this research?

Your alternative is not to take part in this study. If you choose not to take part in this study, your future care will not be affected. If you do not wish to take part in this research study, you will receive treatment according to the standard of care policy and your care will in no way be put at risk.

What happens if I say yes, but I change my mind later?

You can leave the research at any time and it will not be held against you. However, if you decide to stop participating in the study, we encourage you to talk to the study doctor first. If you stop being in the research study after the pain injection is completed, it cannot be reversed nor will you be able to switch to the other study group. However, you will be able to choose an alternate pain control method. Additionally already collected data may not be removed from the study database. You will be asked

whether the investigator can collect data from your routine medical care. If you agree, this data will be handled the same as research data.

Is there any way being in this study could be bad for me?

The pain medication administration will be performed in the emergency room at UC Davis Medical Center using the standard process used in those with hip fractures. The two medications that could be given have some distinct negative reactions that can occur.

After being given liposomal bupivacaine, very common reactions include nausea, vomiting and constipation. Common reactions include things such as fever, dizziness, swelling of the hands and feet, headache, difficulty sleeping, pain at the site of injection, low blood levels and back pain.

After being given ropivacaine, very common reactions include nausea, vomiting and low blood pressure. Common reactions include a low heart rate, fever, pain at the site of injection, low blood levels, inability to urinate, dizziness, high blood pressure, chest pain, shortness of breath, bladder infections and muscle cramps.

Additional side effects can occur from both the study medication (liposomal bupivacaine) and ropivcaine such as an allergic reaction or when the amount of medication in the blood becomes too high.

Allergic reactions to the medication range from minor to severe. Minor reactions include itching, rash, and swelling at the site of administration. Severe reactions include a fast heart beat, dizziness, nausea, fainting, severe swelling, weakening of cartilage, difficulty breathing and a low blood pressure.

If either of the medications are injected into a blood vessel or absorbed too quickly, abnormally high blood levels can occur and can have effects on your heart and nervous system. Heart symptoms include a rapid and/or an irregular heart rate. In rare circumstances, this irregular heart rate can be life threatening—even to the point of cardiac arrest (abrupt loss of heart function) and requires immediate action to treat. Nervous system reactions also range from minor to severe. Minor reactions include numbness, nervousness, nausea, ringing in your ears, blurry vision or restlessness. Severe reactions can include shaking and even seizure and coma which require immediate treatment.. The safety of both of these medications, ropivacaine and liposomal bupivacaine have been studied and are approved by the Federal Drug Administration. Rarely, the drug can decrease the ability of your blood to bind oxygen(methemoglobinemia). The safety profile of the study medication, liposomal bupivacaine, does not appear to differ from standard local medication. Regardless of your treatment group, you will be monitored closely following the injection of the medication for any abnormal reactions and treated as needed.

There may also be risks to your privacy. The Researchers will store study records and other information about you in a secure location and will grant access only to those with a need to know. However, just like with other personal information kept by your health care providers, your banks, and others, even these safeguards cannot guarantee absolute protection of the data. If private information gets into the wrong hands, it can cause harm. Although rare, there are reported cases of breaches that have resulted in discrimination in insurance or employment.

Randomization Risk

You will be assigned to a treatment program by chance, and the treatment you receive may prove to be less effective or to have more side effects than the other study treatment or other available treatments.

Will being in this study help me in any way?

We cannot promise any benefits to you or others from your taking part in this research. However, possible benefits include improvement in pain management and the use of fewer oral pain medications. The use of less oral pain medications may decrease chances of common side effects occurring such as slowing your breathing rate, drowsiness and constipation. Additionally, improved pain control may speed your recovery.

What happens to the information collected for the research?

Efforts will be made to limit use or disclosure of your personal information, including research study and medical records, to people who have a need to review this information. We cannot promise complete confidentiality. Organizations that may inspect and copy your information include the IRB and other University of California representatives responsible for the management or oversight of this study. Department of Defense representatives may also review (or have access to) your research record as part of their responsibility to protect human volunteers in research.

The monitors, auditors, the IRB, the Food and Drug Administration will be granted direct access to your research records to conduct and oversee the study. We may publish the results of this research. However, we will keep your name and other identifying information confidential.

A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.

If we access protected health information (e.g., your medical record), you will be asked to sign a separate form to give your permission. Your medical records may become part of the research record. If that happens, your research records may be looked at by the sponsor of this study and government agencies or other groups associated with the study. They may not copy or take your personal health information from your medical records unless permitted or required by law.

Federal law provides additional protections of your medical records and related health information. These are described in the UC Davis Health System Notice of Privacy Practices (http://www.ucdmc.ucdavis.edu/compliance/pdf/notice.pdf) and in an attached document.

Can I be removed from the research without my OK?

The person in charge of the research study can remove you from the research study without your approval. Possible reasons for removal include the following:

- If you do not follow the study doctor's instructions
- If we find out you should not be in the study

- If the study is stopped
- If it becomes harmful to your health

If you are withdrawn from the research, the data collected on you to the point of withdrawal remains part of the study database and may be included in the data analysis. If you leave the study, no more information about you will be collected for this study.

We will tell you about any new information that may affect your health, welfare, or choice to stay in the research.

What else do I need to know?

This research is being funded by United States Department of Defense, also called the sponsor.

There is no charge for you to participate in this study. Neither you nor your insurance carrier will be charged for your taking part in the research. All costs associated with the study will be paid by the sponsor/department.

You or your health plan will be billed for the costs of routine medical care you receive during the study. These costs may include operating room fees, pharmacy charges, treatments, hospitalization, scans, etc. You will be expected to pay for the usual deductibles and co-payments, and for any routine care that is not covered.

For more information about possible costs, please contact the research team. The research team can follow UC Davis Uninsured Non-Emergency Estimate Policy (Policy ID 1883) to work with their department and Decision Support Services to get you a cost estimate.

It is important that you promptly tell the person in charge of the research if you believe that you have been injured because of taking part in this study. If you are injured as a result of being in this study, the University of California will provide necessary medical treatment. Depending on the circumstances, the costs of the treatment may be covered by University or the study sponsor or may be billed to your insurance company just like other medical costs. The University and the study sponsor do not normally provide any other form of compensation for injury.

You will not be compensated for taking part in this study.

For more information about compensation, you may call the IRB Administration at (916) 703-9151 or email at IRBAdmin@ucdmc.ucdavis.edu

Signature Block for Capable Adult

Your signature documents your permission to take part in this research.

Signature of subject	Date
Printed name of subject	
Signature of person obtaining consent	Date
Printed name of person obtaining consent	

Witness to sign only as applicable i.e. for short form of consent documentation or illiterate subjects.

My signature below documents that the information in the consent document and any other written information was accurately explained to, and apparently understood by, the subject, and that consent was freely given by the subject.

Signature of witness to consent process	Date
Printed name of person witnessing consent process	